What's hot, what's new

– ESPN 2015

Introduction

As the 'CME team' for the ESPN we have put together a series of key work presented at the ESPN.

'What's hot, what's new' includes a glimpse at some of the important papers, invited talks and posters presented at the meeting.

This is NOT an exhaustive list of all the presentations. If you have seen any other important presentations, please do let us know and we will share them on our CME website.

Inherited kidney disease

- It is known that children with **Autosomal dominant poycystic kidney disease** (**ADPKD**) should be followed for hypertension and treated with angiotensin-converting enzyme inhibitor (ACEi) even with borderline hypertension (75th to 95th percentile of blood pressure) because of the increase risk of left ventricular mass index and long-term potential for cardiovascular damage. F. Emma presented the **ADPKids European cohort** of more than **300 ADPKD children.** He demonstrated that 24hours Ambulatory Blood Pressure Monitoring (**ABPM**) in ADPKD patients have a **non-dipping pattern.** Whether we need to treat for this remains a question?

- Dr**ugs** in **adult ADPKD** - presented by Y. Pirson. **Tolvaptan**, an AVP-V2 receptor inhibitor demonstrated good results in slowing disease progression in adults, however with side effects! Knowing that renal injury begins with the formation of the first cyst, **should we start treating ADPKD children?** No answer yet…, BUT we should **encourage the ADPKD children** to **increased fluid intake**. If interested to read more: **Grantham JJ.** Rationale for early treatment of polycystic kidney disease. **Pediatr Nephrol. 2015 Jul;30(7):1053-62.**

- **Ciliopathies** - C. Bergmann presented the rational for new genetic technologies which have considerably improved genetic research and diagnostics. He presented the results of a **novel customized sequence capture based next-generation sequencing** data on 308 patients with polycystic kidney disease. He proposed a **dosage-sensitive model** for early and severe forms.

Inherited kidney disease - 2

- **Ciliopathies:** K. Van Hoeve and J. Bissler demonstrated that **renal complications** are **very common** in **Tuberous Sclerosis complex (TSC)** disease. Hypertension, proteinuria, CKD are **also present in children.** CKD is mainly due to renal injury, bleeding from angiomyolipomas and surgery (often unnecessary). Also, J. Bissler showed the effect of **Everolimus** (mTORinhibitor) on the reduction of the renal angiomyolipomas. The symposium "TSC: where pediatric neurologists and nephrologists meet" demonstrated the need of a **multidisciplinary clinic**. If interested, please read the **new recommendations** of **follow-up the renal phenotype in TSC patients**. **Krueger DA et al**: International Tuberous Sclerosis Complex Consensus Group surveillance and management. **Pediatr Neurol. 2013. 49:255.**

- **Idiopatic infantile hypercalcemia** (IIH): M. Konrad's group presented the genetic heterogeneity of IIH by the identification of the **recessive *SLC3A1* mutation (NaPi-IIa)** and the importance of distinguishing it from the *CYP24A1* (24-hydroxylase) which is crucial for effective therapy. In the affected *SLC3A1* mutation infants, the clinical and laboratory findings persist after omitting vitamin D but rapidly respond to phosphate supplementation. If interested, read: **Schlingmann KP.** Autosomal-Recessive Mutations in SLC34A1 Encoding Sodium-Phosphate Cotransporter 2A Cause Idiopathic Infantile Hypercalcemia. **J Am Soc Nephrol. 2015.**

- About 20% of the **children with ESRD** do not have a primary renal disease diagnosis. N. Knoers group presented the targeted panel sequence of **399 renal genes (RENome)**. They suggest that this gene panel improves the diagnostic and etiological classification of ESRD.

Immune mediated renal disorders

- **ESPN-ERA-EDTA survey on indications and modalities of renal biopsy in children(A. Amore):** Renal biopsy plays a key role in the diagnosis and management of kidney disease. Since there are no global guidelines on modalities and indications for this diagnostic, prognostic and relatively safe test; a survey was designed by ESPN immune mediated renal disorders WG and ERA-EDTA immunonephrology WG in order to receive detailed data. 629 questionnaires (229 pediatric nephrologist) were filled – this is the largest survey on renal biopsy procedure and clinical indications.

- **Lupus Nephritis (R Topaloglu):** Classification, clinical properties, treatment modalities and new medications of childhood lupus nephritis were presented.

- A multi centric project about pediatric lupus nephritis patients' treatment schedule and long term outcomes have been proposed. The project aims to compare the efficiency and safety of different drug regimes along with the identification of factors associated with response to induction therapy and number of relapses.

Immune mediated renal disorders

- **Complement involvement in primary glomerular diseases(JC Davin):** The role of the complement pathways in glomerulonephritis especially lupus nephritis, membranoproliferative glomerulonephritis, C3 glomerulopathy, DDD and IgA nephritis were presented. New classification of complement disregulation associated MPGN (IC-mediated and C3 glomerulopaty) was given. Treatment modalities of C3 glomerulopathy and IgA nephritis and the effectiveness of anti C5 Ab treatment were discussed.

- **New drugs entering in the portfolio for the treatments of immune mediated glomerular diseases (R Coppo):**Effects of proteasome inhibitors in renal disease were presented. Proteasome is a protein degradation system, plays a crucial role in cell cycle progression and apoptosis; activation of transcription factors, cytokines and chemokines. Proteasome proteolysis is essential for the degradation of the inhibitory protein NF-kB. NF-kB inhibition can reduce the expression of many genes encoding key inflammatory mediators, such as TNF, IL-1 ICAM, VCAM and enzymes.
- PS inhibitors are potentially indicated for most immune-mediated renal diseases. PS inhibitors are being adopted in pilot studies in antibody-mediated renal rejection and in AL amyloidosis, lupus, IgA nephropathy, idiopathic nephrotic syndrome and renal fibrosis.

CAKUT

Mutations in TBX18 Cause Dominant Urinary Tract Malformations via Transcriptional Dysregulation of Ureter Development

The American Journal of Human Genetics 97,291-301,August 6,2015

- CAKUT : 3-6/1000 L life birth 20-30% of all prenatal malformations
- Many CAKUT forms are caused by single gene defect even if the important heterogeneity make gene identification very difficult.
- Whole Exome sequencing in 4 generations family with ADCAKUT allows identification of Tbx18 , member of Tbx1 transcription factor genes implicated in nephrogenesis
- Tbx18 interfere with transcriptional repression: cells not differentiate in smooth muscle cells of the ureter instead differentiate into fibroblasts-like cells in the kidney.
- Tbx18 -/- ; Tbx18 +/- mice develop enlarged uretera and hydronephrosis
- **Conclusion:** Dominant TBX18 mutations as causing human CAKUT via lack of repression of TBX18 transcriptional activity for the first time implicates ureter smooth muscle cell development in the pathogenesis of human CAKUT

CAKUT - 2

The HNF1 score is a simple tool to select patients for HNF1 gene analysis

- *Kidney International (2014) 86, 1007-1015*
- AD inheritance with 50% of de novo mutation and the first cause of hypoplastic kidney
- Due to phenotype variability, to identify patients susceptible to present HNF1 mutation is challenging and often under diagnosed
- Authors proposed a HNF1a score witch includes 17 items (antenatal data, filmily history, organ involvement (a score ≥ 8 consider HNF1B gene analysis)
- This score is suitable for young patients who present most of the time with isolated renal malformations

Table 2 | *HNF1B* score

Characteristics	Item	Value
Family history		+2
Antenatal renal abnormalities	Uni/bilateral abnormality by renal echography	+2
Kidneys and urinary tract		
Left kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Right kidney	Hyperechogenicity	+4
	Renal cysts	+4
	Hypoplasia	+2
	Multicystic and dysplastic kidney	+2
	Urinary tract malformation	+1
	Solitary kidney	+1
Electrolyte or uric acid disorders	Low serum Mg^{2+} (<0.7 mmol/l)	+2
	Low serum K^{+} (<3.5 mmol/l)	+1
	Early-onset gout (>30 years of age)	+2
Pathological findings	Oligomeganephronia or glomerular cysts	+1
Pancreas[a]	MODY or hypoplasia of tail and neck of the pancreas or pancreatic exocrine insufficiency	+4
Genital tract	Genital tract abnormality[b]	+4
Liver	Live test abnormalities of unknown origin[c]	+2

Abbreviations: HNF1, hepatocyte nuclear factor-1; MODY, maturity-onset diabetes of the young.
This score should be assessed after ruling out easily recognizable inherited renal diseases (i.e., autosomal-dominant or -recessive polycystic kidney disease and renal-coloboma syndrome).
[a]Maximal value of the item pancreas is 4.
[b]Bicornuate uterus, hemiuterus, uterus and upper vagina aplasia, epididymal cysts, bilateral absence of vas deferens.
[c]After exclusion of autoimmune, toxic, or viral hepatitis.

Idiopathic nephrotic syndrome

- The role of B cells in INS: memory B cells are depleted by rituximab and their recovery is delayed in patients who remain in remission

- B cell depletion is an efficient treatement to prevent relapses in the majority of steroid dependent patients but severe infectious complications occurred in large series

- Exome sequencing either done in families with autosomal dominant or recessive inheritance of idiopathic nephrotic syndrome failed to link the disease with a locus or a limited set of genes

- Levamisole is definitely a useful drug in the management of steroid dependent patients while it significantly delays the relapse after prednisone withdrawal

- PACAP is playing a major role in the mechanism of thrombosis during relapse and supports the use of anti-aggregation drugs

Nutrition and CKD

- **Data from CKID for dietary requirements (B Warady)**: 20% of CKD children are overweight. Protein and sodium intakes are significantly greater than daily recommended intake.

- **Data from the IPPN (B Warady)**: 45% of CKD children present hyperphosphatemia.

- **Take-home message (B Warady, De Guchtenaere)**: nutritional support is really important to avoid under-weight BUT we also should be able to reevaluate patients to avoid over-weight.

- **The role of uremic toxins derived from p-cresol and metabolized in the gut (R Vanholder)**: will be able in a near future to modulate this 'gut-kidney' axis in pediatric CKD?

- **The phosphate educational program (PEP) in pediatric CKD (Ahlenstiel)** : when the use of phosphate binders is adapted to the phosphate content in food. An interesting concept derived from endocrinologists who adapt insulin dose depending on the glucose content in food

Bone and cardiovascular disorders in CKD

- **Breaking news on pathophysiology (I Salusky)** : normal mice and mice with CKD that are put on a high iron diet display decreased phosphate levels and decreased FGF23 levels .

- **Iron as an inhibitor of FGF23?** Will this new pathway be relevant in CKD-MBD management in a near future?

- In this setting, **new phosphate binders** (iron-based) have been recently approved and are used in adults with CKD

- **Phosphate** is a vascular toxin, we should fight to keep phosphate levels within the normal range **(R Shroff)**.

- **In obese children,** diet may improve endothelial dysfunction, but the association of diet + exercise is far better **(F Mallamaci)**.

- **Vitamin D** has a role in bone and phosphate/calcium metabolism, but also beneficial effects on immunity, inflammation, iron homeostasis and progression of renal disease **(J Bacchetta)**.

Dialysis

- **Protecting the morphology and function of the peritoneal membrane** – C Aufricht

Discussed inflammatory mechanisms in the initiation and establishment of peritoneal inflammation and in vitro data on a novel PD solution that may reduce inflammation driven peritoneal sclerosis and fibrosis.

For more details read Herzog R et al; J Am Soc Nephrol. 2014. doi: 10.1681/ASN.2013101128.

- **Carpediem for infants with dialysis dependent AKI or CKD** – C Ronco and J Vande Walle:

Introducing the Carpediem for CRRT in infants – The main characteristics of Carpediem are the low priming volume of the circuit (less than 30 mL), miniaturised roller pumps, and accurate ultrafiltration control via calibrated scales with a precision of 1 g.

For more details read Ronco et al, Lancet. 2014. doi: 10.1016/S0140-6736(14)60799-6.

- **Haemodiafiltration: a superior dialysis modality?** M Fischbach and R Shroff

Randomised controlled trails in adults on HDF have shown a significant reduction in all-cause and cardiovascular mortality on HDF compared to HD. An international multicentre study comparing cardiovascular and growth outcomes in children on HDF vs conventional HD is ongoing, currently recruiting from >10 countries in the EU.

For more details read Mostovaya IM et al, Seminars in Dialysis 2014. PMID: 24738146

Dialysis – 2 (Abstracts and Plenary session)

- **Concept of Adapted automated PD** – A Zaloszyc

Delivering the same amount of dialysate (2L/m2) over the same duration (150min) applying a short small cycle before a long large cycle compared to the repetition of two identical cycles in terms of dwell/fill may lead to improved sodium removal and ultrafiltration. A multicentre study has been planned to test this concept.

- **Association of early fluid overload and AKI** – L Yanghong

In a cohort of 370 children early fluid overload independently predicted PICU mortality in critically ill children.

- **Peritoneal membrane in health, uraemia and PD** – B Schaefer

A global paediatric peritoneal biobank has been established. The healthy peritoneum exhibits substantial age dependent characteristics which disappear during PD. Major time-dependent peritoneal membrane transformation develops with low GDP dialysis, albeit is less pronounced than with high GDP fluid usage.

- **Plenary symposium – ethics of transplanting children with severe disabilities:**

A very interesting session presented by clinicians, epidemiologists and ethicists discussing the suitability of dialysis and transplantation in severely disabled children.
For a recent review on the topic read Goldberg AM, Amaral S, Moudgil A. Developing a framework for evaluating kidney transplantation candidacy in children with multiple comorbidities. Pediatr Nephrol. 2015. doi: 10.1007/s00467-013-2704-4.

Renal transplant

- Claas: precise characterization and quantification of donor specific antibodies is a now routine practice. However, doubts are arising about the clinical significance of the results. What level of antibodies is clearly detrimental? How do we balance the long term dialysis damages versus the possible risk of a humoral chronic rejection if we accept a kidney in a child who carries (very) low titers antibody against that kidney? Test to identify complement binding properties of these antibodies may be necessary and it is possible that we'll be asked to consider as unremarkable very low intensity DSA.

- Dello Strologo: desensitization is a feasible strategy with several different procedures. Short and intermediate results are quite good but long-term results are disappointing. Humoral chronic rejection almost invariably occurs. Nationwide efforts to provide carefully matched kidney should be implemented.

Renal transplant - 2

- Toenshoff: for pediatric recipients, it is important to find a good compromise between HLA compatibility and waiting time.

Compared with recipients of 2–3 MM first grafts, 4–6 MM graft recipients spent 12% less time and 0–1 MM recipients 15% more time with a functioning graft after the first transplant. Outcomes only begin to diverge between the 2–3 and 4–6 HLA MM categories after about 12 years, when failures are more prevalent. The inevitable trade-offs between waiting time and HLA MM must be carefully weighed.

The potential relatively small benefit of greater HLA matching may not be justifiable during the critical developmental intervals of childhood and adolescence, because longer waits for a first graft may be required if HLA matching were to be prioritized in allocation.

Renal transplant – 3 (Abstracts)

- Kuypers: pharmacogenetics is a very challenging issue which might explain important interindividual differences in immunosuppressive drugs dosing. Moreover, in patients who require significantly higher dosage of drugs to achieve satisfactory plasma level, active metabolites might also account for renal toxicity.

- Stojanovic: ABOi transplantation in children have good outcome with graft survival and rejection rates comparable to ABO compatible transplants.

- Marks: HLA incompatible renal transplantation from a living donor is a feasible option for a sensitised child

- Goh: Greater intraoperative fluid volumes and post-transplant fluid balance are associated with higher Systolic Blood Pressure (SBP) z scores. Both higher pre-transplant SBP z scores and greater intraoperative fluid volumes are associated with improved GFR.

- Trautmann: Risk factors for post-transplant Recurrence of steroid resistant nephrotic Syndrome (srns): results from the podonet Registry: detection of a genetic diagnosis remains the only relevant predictive criterion in risk evaluation of post-transplant disease recurrence in children with SRNS.

- Dufek: Plasma cell rich acute rejection episodes in pRTR are associated with reduced renal allograft survival

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